



EP 1 717 235 A3

(12)

EUROPEAN PATENT APPLICATION

(88) Date of publication A3:
28.02.2007 Bulletin 2007/09

(51) Int Cl.:
C07D 295/088 (2006.01) **C07D 213/30** (2006.01)
C07D 211/68 (2006.01) **C07D 333/16** (2006.01)
C07D 211/14 (2006.01) **C07D 401/10** (2006.01)
A61K 31/40 (2006.01) **A61K 31/44** (2006.01)
A61K 31/381 (2006.01) **A61K 31/5377** (2006.01)
A61P 25/00 (2006.01)

(43) Date of publication A2:
02.11.2006 Bulletin 2006/44

(21) Application number: 05291793.7

(22) Date of filing: 26.08.2005

(84) Designated Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR
HU IE IS IT LI LT LU LV MC NL PL PT RO SE SI
SK TR

Designated Extension States:
AL BA HR MK YU

(30) Priority: 29.04.2005 EP 05290950

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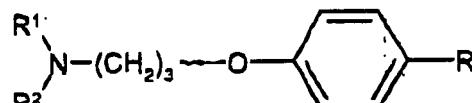
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(54) **Phenoxypropylpiperidines and -pyrrolidines and their use as histamine H3-receptor ligands**

(57) The present patent application concerns compounds of formula (I),



(I)

with R¹ and R² taken together with the nitrogen atom to which they are attached, form a mono or bicyclic saturated nitrogen-containing ring;
 their preparation and their use as a H3 receptor ligand for treating e.g. CNS disorders like Alzheimer's disease.



DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (IPC)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
D, X	WO 00/06254 A (SOCIETE CIVILE BIOPROJET; SCHWARTZ, JEAN-CHARLES; ARRANG, JEAN-MICHEL;) 10 February 2000 (2000-02-10) * claims 1,4-7,16,18,23,24,26,79-87; examples 44,48,59,65,74,90,93,96,104,111 * * page 55, line 15 - page 56, line 25 * -----	1-3,5, 11, 14-20, 23,25	INV. C07D295/088 C07D213/30 C07D211/68 C07D333/16 C07D211/14 C07D401/10 A61K31/40 A61K31/44 A61K31/381 A61K31/5377 A61P25/00
X	WO 2004/037788 A (GLAXO GROUP LIMITED; BEST, DESMOND, JOHN; ORLEK, BARRY, SIDNEY) 6 May 2004 (2004-05-06) * claims 1,4,6,8,11,12,23; examples 1-4,8-65 * * page 9, line 11 - line 25 * -----	1,2,11, 14-23,25	
X	WO 02/076925 A (ELI LILLY AND COMPANY; BEAVERS, LISA, SELSAM; GADSKI, ROBERT, ALAN; HI) 3 October 2002 (2002-10-03) * claims 1,7,14,21,22; examples 216,227,236,269,270,297-301 * * page 1, line 6 - line 22 * -----	1-3,5, 13, 15-23,25	TECHNICAL FIELDS SEARCHED (IPC)
X	US 4 950 674 A (YANNI ET AL) 21 August 1990 (1990-08-21) * abstract; examples 53,90,182; table 1 * -----	1,3,5, 14,15,25	C07D A61K
X	KUBOTA, HIDEKI ET AL.: J. MED. CHEM., vol. 46, 2003, pages 4728-4740, XP002355168 * page 4729; table 2; compound 10S * ----- -/-	1,3,14, 15	
6 The present search report has been drawn up for all claims			
Place of search		Date of completion of the search	Examiner
Berlin		15 August 2006	Krische, Detlef
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document			
T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			



DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (IPC)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	WO 99/59959 A (ZENECA LIMITED; BROWN, DEARG, SUTHERLAND; BROWN, GEORGE, ROBERT) 25 November 1999 (1999-11-25) * example 5; table I; compound 3 * * example 6 * * example 7; table II; compounds 38,41,42 * * page 54, line 16 - line 20 * ----- X EP 0 382 185 A (OTSUKA PHARMACEUTICAL CO., LTD) 16 August 1990 (1990-08-16) * abstract * * examples 111,115,332; table 1 * * examples 450-456; table 3 * ----- X YOSHIDA K ET AL: "Synthesis of Benzanilide Derivatives as Dual Acting Agents with alpha1-Adrenoceptor Antagonistic Action and Steroid 5-alpha Reductase Inhibitory Activity" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 8, no. 21, 3 November 1998 (1998-11-03), pages 2967-2972, XP004141855 ISSN: 0960-894X * abstract; figure 1; compound 1 * * table 1; compound 5C * * scheme 1 * ----- X WO 2004/037800 A (GLAXO GROUP LIMITED; BEST, DESMOND, JOHN; BRUTON, GORDON; HEIGHTMAN, T) 6 May 2004 (2004-05-06) * claim 1; examples 1-51,57-114,123,124,147-152,156-162,172 * * page 17, line 30 - page 18, line 13 * * page 8, line 30 - page 10, line 25 * ----- Y -/-	1,2,13, 15,25 1,3,15 1,14,15	TECHNICAL FIELDS SEARCHED (IPC)
6	The present search report has been drawn up for all claims	1-3,11, 14-23,25 24,26	
Place of search		Date of completion of the search	Examiner
Berlin		15 August 2006	Krische, Detlef
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T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			



DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (IPC)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
Y	WO 03/059342 A (ABBOTT LABORATORIES) 24 July 2003 (2003-07-24) * page 1, line 3 - line 5; claim 1 *	24	
Y	----- WO 01/74815 A (ORTHO MCNEIL PHARMACEUTICAL, INC) 11 October 2001 (2001-10-11) * page 1, line 21 - page 2, line 6 *	26	
E	----- WO 2005/089747 A (SERVIER LAB [FR]; CASARA PATRICK [FR]; CHOLLET ANNE-MARIE [FR]; DHAINA) 29 September 2005 (2005-09-29) * abstract; claims 1,8,12,13,23,24,31-36; examples 6,9,11-15,17,22,51,52,57-61,84-93,104-106 * * page 48, line 4 - line 10 *	1,3,5, 11, 14-21, 23,25	
E	----- WO 2005/100321 A (MILLENNIUM PHARMACEUTICALS, INC; GHOSH, SHOMIR; ELDER, AMY, M; CARSON,) 27 October 2005 (2005-10-27) * table 3; compounds C103, C104 * * table 9; compounds H28,H76,H118,H129,H132,H149 * * page 44, paragraph 147 *	1,11,13, 15,25	TECHNICAL FIELDS SEARCHED (IPC)
A	----- PESCHKE, BERND ET AL.: BIOORGANIC & MEDICINAL CHEMISTRY, vol. 12, 2004, pages 2603-2616, XP002355169 * abstract * * page 2609 - page 2610 *	16	
A	----- HILTMANN, R. ET AL.: SYNTHESIS, 1971, pages 213-214, XP002355170 * the whole document *	1	
The present search report has been drawn up for all claims			
6	Place of search Berlin	Date of completion of the search 15 August 2006	Examiner Krische, Detlef
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document			
T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			

**CLAIMS INCURRING FEES**

The present European patent application comprised at the time of filing more than ten claims.

Only part of the claims have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims and for those claims for which claims fees have been paid, namely claim(s):

No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims.

LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

see sheet B

All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.

As all searchable claims could be searched without effort justifying an additional fee, the Search Division did not invite payment of any additional fee.

Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid, namely claims:

None of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims, namely claims:

1-3, 5, 7, 9, 11-26 in part



The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

1. claims: 1-3,5,7,9,11-26 in part

Compounds of formula (I) having a -CONR₃R₄ group as substituent R for use as H₃-receptor ligands; their preparation and use.

2. claims: 1-3,7,11-26 in part

Compounds of formula (I) having a benzoyl group as substituent R for use as H₃-receptor ligands; their preparation and use.

3. claims: 1-3,5-7,9-26 in part

Compounds of formula (I) having a -C(OH)R₅R₆ group as substituent R for use as H₃-receptor ligands; their preparation and use.

4. claims: 1-3,7,11-26 in part

Compounds of formula (I) having a -CH₂CN group as substituent R for use as H₃-receptor ligands; their preparation and use.

5. claims: 1-3,7,11-26 in part

Compounds of formula (I) having an isoprenyl group as substituent R for use as H₃-receptor ligands; their preparation and use.

6. claims: 1-3,7,11-26 in part

Compounds of formula (I) having a styryl group as substituent R for use as H₃-receptor ligands; their preparation and use.

7. claims: 1-3,7,11-26 in part

Compounds of formula (I) having a phenoxy or benzyloxy group as substituent R for use as H₃-receptor ligands; their preparation and use.

8. claims: 1-26 in part



The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

Compounds of formula (I) having a partially saturated nitrogen containing heterocycle or a nitrogen containing heteroaryl as substituent R for use as H3-receptor ligands; their preparation and use.

9. claims: 1-3,7,11-26 in part

Compounds of formula (I) having a thienyl group as substituent R for use as H3-receptor ligands; their preparation and use.

10. claims: 1-26 in part

Compounds of formula (I) having a phenyl group as substituent R for use as H3-receptor ligands; their preparation and use.

11. claims: 1-26 in part

Compounds of formula (I) having a saturated cycloalkyl group as substituent R for use as H3-receptor ligands; their preparation and use.

12. claims: 1,2,7,11-26 in part

Compounds of formula (I) having an alkyl group substituted by a cycloalkyl group as substituent R for use as H3-receptor ligands; their preparation and use.

13. claims: 1-3,5,7,9,11-26 in part

Compounds of formula (I) having an -alkyl-phenyl-(0)n-X-NR3R4 group as substituent R for use as H3-receptor ligands; their preparation and use.

14. claims: 1,2,7,11-26 in part

Compounds of formula (I) having an alkenyl or alkynyl group substituted by -(CO)-NR3R4 as substituent R for use as H3-receptor ligands; their preparation and use.

15. claims: 1,2,7,11-26 in part



The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

Compounds of formula (I) having a phenylalkyl, phenylalkenyl or phenylalkynyl group substituted by $-(CO)n-NR_3R_4$ as substituent R for use as H3-receptor ligands; their preparation and use.

16. claims: 27,28

Process for preparing intermediate compound of formula (X)

ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.

EP 05 29 1793

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

15-08-2006

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
WO 0006254	A	10-02-2000	AT AT AU CA DE DE DE EP ES ES JP PT PT US	326446 T 276751 T 5511999 A 2321881 A1 69920472 D1 69920472 T2 69931409 T2 0982300 A2 2260703 T3 2226423 T3 2002521463 T 1428820 T 1100503 T 7138413 B1	15-06-2006 15-10-2004 21-02-2000 10-02-2000 28-10-2004 06-10-2005 02-11-2006 01-03-2000 01-11-2006 16-03-2005 16-07-2002 29-09-2006 31-01-2005 21-11-2006
WO 2004037788	A	06-05-2004	AT AU EP JP	346044 T 2003278119 A1 1554243 A1 2006505623 T	15-12-2006 13-05-2004 20-07-2005 16-02-2006
WO 02076925	A	03-10-2002	AU CA EP JP	2002254114 A1 2441080 A1 1379493 A2 2004532834 T	08-10-2002 03-10-2002 14-01-2004 28-10-2004
US 4950674	A	21-08-1990	NONE		
WO 9959959	A	25-11-1999	AT AU AU BR CA CN DE DE EP ES HK HU ID JP NO NZ PL PT RU	282590 T 749293 B2 3939999 A 9910474 A 2328927 A1 1300278 A 69921986 D1 69921986 T2 1077931 A1 2232137 T3 1033754 A1 0102295 A2 26236 A 2002515476 T 20005767 A 507144 A 344164 A1 1077931 T 2215736 C2	15-12-2004 20-06-2002 06-12-1999 02-01-2001 25-11-1999 20-06-2001 23-12-2004 22-12-2005 28-02-2001 16-05-2005 06-05-2005 28-11-2001 07-12-2000 28-05-2002 14-11-2000 25-10-2002 08-10-2001 31-03-2005 10-11-2003

ANNEX TO THE EUROPEAN SEARCH REPORT
ON EUROPEAN PATENT APPLICATION NO.

EP 05 29 1793

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

15-08-2006

Patent document cited in search report	Publication date		Patent family member(s)	Publication date
WO 9959959	A		SK 17182000 A3 TR 200003353 T2 US 6579872 B1	10-05-2001 20-04-2001 17-06-2003
EP 0382185	A 16-08-1990	CN DE DE DK ES HK	1046529 A 69009785 D1 69009785 T2 382185 T3 2056259 T3 1003113 A1	31-10-1990 21-07-1994 03-11-1994 04-07-1994 01-10-1994 09-10-1998
WO 2004037800	A 06-05-2004	AU EP JP US	2003274053 A1 1554260 A1 2006512404 T 2006052597 A1	13-05-2004 20-07-2005 13-04-2006 09-03-2006
WO 03059342	A 24-07-2003	AU CA EP JP MX US	2003235687 A1 2473232 A1 1474132 A1 2006500315 T PA04006777 A 2005113435 A1	30-07-2003 24-07-2003 10-11-2004 05-01-2006 10-11-2004 26-05-2005
WO 0174815	A 11-10-2001	AU EP	4967901 A 1268478 A2	15-10-2001 02-01-2003
WO 2005089747	A 29-09-2005	AR AU CA EP FR	047685 A1 2005224129 A1 2555216 A1 1720544 A1 2866647 A1	01-02-2006 29-09-2005 29-09-2005 15-11-2006 26-08-2005
WO 2005100321	A 27-10-2005	AR AU CA	048528 A1 2005233125 A1 2561564 A1	03-05-2006 27-10-2005 27-10-2005